The amino acid sequences and enzymatic activities of the enzymes that can be used in the claimed methods were known at the time this application was filed. What was not known what the disorders that could be treated, because it was not known that the enzymes were useful to inhibit angiogenesis. One skilled in the art would have no trouble obtaining or using the claimed enzymes.

For example, a review of the specification at page 7, beginning at line 23, makes clear that chondroitinases AC and B from a variety of bacteria and from mammalian sources were known, cloned, isolated and characterized as of the filing date of this application. The activities are similar enough to those of the enzymes isolated from *F. heparinum* that those skilled in the art would have to undertake no more than routine experimentation to practice the claims methods. The law is quite clear that the standard is not whether *some* experimentation is required, but whether it is undue.

However, to facilitate prosecution, the claims have been limited to chondroitinases. Enzymes are categorized based on their substrate specificity. In this case, by limiting to chondrointinases, applicants have defined the critical features that are demonstrated by the examples. The examiner has provided no basis for saying that the chondroitinase isolated from one bacteria or from a mammalian source is any different from a chondroitinase isolated from a different source. The knowledge regarding an "enzyme" is not defined by or limited by its origin (i.e., *F. heparinum*) but by its enzymatic activity and specificity.

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Amendment

Claims 2, 6 and 8 have been amended in response to the examiner's comments to clarify the Markush groups and provide antecedent basis.

Claim 8 has been divided into two claims, claim 8 of a more specific disease scope, and claim 27, drawn to the functionally defined disorders.

Rejections under 35 U.S.C. 102

Claims 1, 2, 6, 8-11, 20, 22 and 23 were rejected under 35 U.S.C. 102(b) as disclosed by U.S. Patent No. 5,567,417 to Sasisekharan, et al. Claims 1, 2, 4-6, and 8 were rejected under 35 U.S.C. 102(b) as disclosed by U.S. Patent No. 4,696,816 to Brown. Claims 1, 2, 4, 5, 9, and 10 were rejected under 35 U.S.C. 102(b) as disclosed by Takeuchi, Br. J. Cancer 26, 115 (1972). These rejections are respectfully traversed if applied to the amended claims.

Claim 1 has been amended to define the disorder as one which is established and characterized by a requirement for angiogenesis.

Claim 10 has been devided into two claims, claim 10 and new claim 26. The examiner has cited no art disclosing topical application of chondroitinase.

The importance of an effective dosage is shown by Example 6 at pages 17-18 and by reference to figure 5, showing that the response is dose-dependent. The prior art does not disclose an effective dosage for inhibiting angiogenesis.

Sasisekharan

Sasisekharan, et al., discloses on the use of heparinase. Sasisekharan does not disclose the use of a chondrointase nor provide any teaching leading one to use a chondroitinase, which

as a different substrate specificity and activity than a heparinase. Nor is there any teaching of what would constitute an effective dosage.

Brown

Brown teaches the use of chondroitinase, as well as collagenase, to break down cartilaginous tissue. See col. 4, lines 25-27 and 42-45. There is no teaching of using chondroitinase or any other glycosaminoglycan degrading enzyme to prevent angiogenesis, which is not cartilaginous tissue but has to do with the migration and proliferation of endothelial cells.

The examiner makes two incorrect statements. The first is that Brown teaches treating a tumor with chondroitinase AC (no citation to where is provided). The ***only*** statement with respect to tumors is found at col. 4, lines 42-45, is as follows:

"The enzyme's pharmaceutical use is not limited to a nucleus pulposus, but should find application in the treatment of ganglia, arthroscopy of joints, certain eye conditions, tumors and other unwanted cartilage tissue."

This statement is not a teaching, but a speculation. There is nothing enabling about it. There is no teaching of the disorder to be treated, how, when or how much enzyme is to be administered, nor even the criteria for success. At best, this is an invitation to experiment. One requiring a great deal of experimentation, particularly since the disclosure relates entirely to degradation of cartilaginous material and the what is claimed is based on inhibition of angiogenesis. ***Cartilage is an avascular tissue!***

The second is that one inherently inhibits angiogenesis merely by administering an enzyme to a site where tumor cells are subsequently injected. As demonstrated by example 6, the effect on angiogenesis is dose dependent. If insufficient enzyme is administered, no efficacy will be observed.

Takeuchi

Takeuchi administers enzyme **prior to or with** tumor cells injected into mice and shows that the tumor cells do not grow as well. Takeuchi does not demonstrate that one can inject enzyme into established tumors and inhibit further growth, nor inhibit angiogenesis – which requires endothelial cells. All of Takeuchi's studies were done solely on and assessing tumor cells.

The examiner's statement that the mechanism is the same since the method steps are the same is not correct. Takeuchi does not inhibit angiogenesis but some other mechanism which prevents the injected cells from forming tumors. The data at col. 1 of page 118 and the discussion at col. 1, of page 119, indicates that the proposed mechanism has nothing to do with angiogenesis. Indeed, the examiner is directed to the second paragraph of the summary on page 1, stating that chondroitin sulphate promotes tumor growth. One skilled in the art would reasonably infer from this that it is the cleavage of chondroitin sulfate at the site of injection that limits tumor growth.

The examiner's attention is drawn to example 7, page 18, and Figures 6 and 7. This demonstrates that the enzyme (1) must be provided in an effective dosage and (2) that it must be

provided in an effective dosage to inhibit multiple activities that are issues with established tumor cells, that are not issues for isolated cells. These include tumor cell invasion, endothelial proliferation and angiogenesis. Those skilled in the art know that merely inhibiting tumor cell growth at an injected site, rather than established disease, means nothing. Indeed, the lower dosages were most relevant to tumor cell proliferation, not angiogenesis.

Many laboratory mice have been cured under the same conditions Takeuchi, uses. There is not much need to cure laboratory mice that were healthy until injected with tumor cells. There is a real need to treat patients who come in with established disease - disease that does not respond to surgery or chemotherapeutic agents. Disease that remains resistant because it is already deeply established within its host. See Example 9 showing that the claimed method is different from that shown by Takeuchi since it shows one can treat ***established, palpable*** tumors as claimed and still be effective.

Rejection under 35 U.S.C. 103

Claims 1-11 and 19-25 were rejected under 35 U.S.C. 103 as obvious over Takeuchi or Sasisekharan, et al. or Brown or WO 96/01648 by Ibex Corporation.JP 51075042. These rejections are respectfully traversed.

All references other than the Ibex PCT are discussed above.

A search of the Ibex application fails to uncover the term "angiogenesis". The Ibex application makes no mention of inhibiting blood vessel growth, migration or proliferation. The Ibex

application fails to disclose any disorder characterized by and dependent upon angiogenesis. Therefore the Ibex application makes up for no deficiencies in any of the cited art.

A rejection under 35 U.S.C. 103 requires that the prior art disclose the claimed subject matter, the motivation to combine as applicants have done, with a reasonable expectation of success.

The prior art does not teach that chondroitinases can inhibit blood vessel growth, migration or proliferation.

The prior art does not teach what an effective amount of enzyme would be to inhibit angiogenesis. As the data in the application demonstrates, dosage is critical - and it is not obvious. The correct dosage must be empiracally determined - not for the disease, but for the mechanism by which it is to be treated - in this case, by limiting the blood vessels that feed the disease.

There is no motivation to combine the elements defined by applicants' claims, much less to treat the disorders as defined by claim 8, or in treating tumors as defined by claims 6, 7, and 21. There is no teaching in any of the references to administer enzyme systemically, or in controlled or sustained release forms. There is no teaching to use chondroitin B to treat a disorder characterized by angiogenesis. There is no teaching of any combination therapy.

Even if motivation to combine, and the elements missing from the cited art, were suddenly to appear, there is nothing that would lead one to any expectation of success. In the field of cancer, there is no expectation of success based on studies in which tumors are treated *ex*

vivo, or at the same time as they are injected into an animal. The literature is replete with failures based on such data. This data is simply not predictive of success in treating established tumors. Therefore the cited references do not make obvious claims 1-11 and 19-25 or new claims 26 and 27.

Allowance of claims 1-11 and 19-25, as amended, and new claims 26 and 27, is therefore earnestly solicited.

Respectfully submitted,

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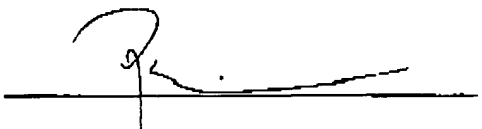
I hereby certify that this Amendment and all accompanying papers were facsimile trasmitted to the Assistant Commissioner of Patents on December 23, 2002.



Patrea Pabst

APPENDIX: Claims marked as Amended

1. (three times amended) A method to decrease angiogenesis comprising administering to a site in an individual in need of treatment thereof for an established disorder requiring angiogenesis an effective amount of a purified [glycosaminoglycan degrading enzyme] chondroitinase to decrease angiogenesis at the site, wherein the decrease in angiogenesis is measured as a decrease in endothelial cell proliferation or a decrease in the formation of capillary-like structures.

2. (amended) The method of claim 1 wherein the enzyme is selected from the group consisting of [bacterial glycosaminoglycan degrading enzyme is selected from the group consisting of heparinase 1 from *Flavobacterium heparinum*, heparinase 2 from *Flavobacterium heparinum*, heparinase 3 from *Flavobacterium heparinum*,] chondroitinase AC from *Flavobacterium heparinum*, [and] chondroitinase B from *Flavobacterium heparinum*, [heparinase from *Bacteroides* strains, heparinase from *Flavobacterium* Hp206, heparinase from *Cytophagia* species,] a chrondoitin sulfate degrading [enzymes] enzyme from *Bacteroides* species, a chrondoitin sulfate degrading [enzymes] enzyme from *Proteus vulgaris*, a chrondoitin sulfate degrading [enzymes] enzyme from *Micrococcus*, a chrondoitin sulfate degrading [enzymes] enzyme from *Vibrio* species, a chrondoitin sulfate degrading [enzymes] enzyme from *Arthrobacter aurescens*, these enzymes expressed from recombinant nucleotide sequences in bacteria and combinations thereof.

3. The method of claim 1 wherein the enzyme is a mammalian enzyme.

4. (amended) The method of claim [1] 8 wherein the enzyme is a chrondroitinase AC.

5. (amended) The method of claim [4] 1 wherein the chondroitinase is chondroitinase AC.

6. (twice amended) The method of claim 1 wherein [at the time] the enzyme is administered to an [the] individual [has] having cancer as evidenced by palpable tumors.

7. The method of claim 6 wherein the cancer is a solid tumor and the enzyme is chondroitinase AC.

8. (amended) The method of claim 1 wherein the individual has a disorder in which angiogenesis is involved, the disorder being selected from the group consisting of rheumatoid arthritis; psoriasis; ocular angiogenic [diseases] disease, rubeosis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; [disease of excessive or abnormal stimulation of endothelial cells,] Crohn's disease, atherosclerosis, scleroderma, [and] hypertrophic [scars] scarring, [diseases that have angiogenesis as a pathologic consequence,] adhesions, [scarring following transplantation,] cirrhosis of the liver, pulmonary fibrosis following acute respiratory distress syndrom or other pulmonary fibrosis of the newborn, endometriosis, polyposis, obesity, uterine fibroids, prostatic hypertrophy, and amyloidosis.

9. The method of claim 1 wherein the enzyme is administered systemically.

10. (amended) The method of claim 1 wherein the enzyme is administered [topically or] locally at or adjacent a site in need of treatment.

11. The method of claim 1 wherein the enzyme is administered in a controlled and/or sustained release formulation.

19. The method of claim 7 wherein the dosage is in the range of 0.1 to 250 IU chondroitinase AC/tumor for tumors in the size range from 20 mm^3 to 15 cm^3.

20. The method of claim 1 wherein the enzyme is administered in combination with another active agent selected from the group consisting of antibiotics, cytokines, cytotoxic agents, and anti-inflammatories.

21. The method of claim 7 wherein the enzyme is administered after excision of the tumor.

22. The method of claim 9 wherein the enzyme is administered by a route selected from the group consisting of intravenous, intra-cranial, and depo.

23. The method of claim 9 wherein the enzyme is administered using an infusion pump.

24. The method of claim 1 wherein the enzyme is chondroitinase B.

25. The method of claim 8 wherein the enzyme is chondroitinase B.

Please add new claims 26 and 27:

26. The method of claim 1 wherein the individual has a disorder in which angiogenesis is involved, the disorder being selected from the group consisting of disease of

excessive or abnormal stimulation of endothelial cells, diseases that have angiogenesis as a pathologic consequence, and scarring following transplantation,

27. The method of claim 1 wherein the enzyme is administered topically.